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(54) Title: POLYVINYL ALCOHOL/BORATE OPHTHALMIC DRUG DELIVERY SYSTEM

(57) Abstract

An aqueous polyvinyl alcohol (PVA)/borate drug delivery system is liquid at low pH values, but gels when the pH is raised to over 7. Such a system affords a method for introducing a liquid containing an ophthalmic drug into the eye cavity, having the liquid carrier system gel under the pH conditions of the eye to allow a sustained, prolonged release of the drug at the desired site in the eye.

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POLYVINYL ALCOHOL/BORATE OPHTHALMIC DRUG DELIVERY SYSTEM

This invention pertains to an aqueous polyvinyl alcohol (PVA)/borate drug delivery system which is liquid at low pH values, but gels when placed in the eye. Such a system is an efficient carrier for an ophthalmic drug allowing for its controlled release and increased duration or retention time from the gelled carrier in the eye.

Most ophthalmic medicaments are topically administered to the eye. The most common dosage form for such medicaments is liquid drops. The liquid drop form is easy to apply, but suffers from the inherent disadvantage that the drug it contains is rapidly washed from the precorneal ocular cavity by blinking and tear flow. Thus, a continued sustained drug level is not obtained. Sustained levels are typically attained only by periodic application of the drops, but this results in frequent administrations by the patient. The result of frequent administration and washing by tear flow or blinking is that the level of medication surges to a peak at the time the drops are applied, then the concentration falls rapidly thereafter.

Other methods of applying ophthalmic medicaments are the unitary ocular inserts. While such inserts deliver the drug in a sustained manner, they suffer from the disadvantages of being difficult to insert and remove and are expensive.

U.S. Patent No. 4,615,697 describes a controlled release ophthalmic bioadhesive composition wherein the ophthalmic drug is embedded in a matrix of polymerized acrylic acid crosslinked with 2,5-dimethyl-1,5-hexadiene. This material is then suspended in a aqueous ophthalmic solution for treatment of the eye.

U.S. Patent No. 4,888,168 discloses a stable ophthalmic aqueous composition for topical administration which comprises a preformed aqueous gel or a gel-forming liquid capable of forming a gel in situ at a pH of less than 5.0. The gel-forming matrix is a high molecular weight poly(acrylic acid), an ethylene/maleic anhydride polymer or a cellulose ether such a hydroxypropylmethyl cellulose.

PCT application WO 89/06964 describes polymers of acrylic acid lightly crosslinked with 3,4-dihydroxy-1,5-hexadiene suspended in aqueous medium at a pH of 3.0 to 6.5 to give a

topical ophthalmic medicament delivery system of sufficiently low viscosity to be administered in drop form. The suspension "gels" when placed in the eye after coming in contact with tear fluid to give a much higher viscosity (clearly still a fluid not a true gel) allowing the suspended medicament to remain in place for a prolonged period of time to provide a sustained release of the medicament.

U.S. Patent No. 4,255,415 describes a long-acting, topical ophthalmic medicament which has a pH that is compatible with even injured eyes which comprises an ophthalmic gel maintained at a pH of 6.5-8.5 containing 0.05-10 % by weight of an ophthalmic medicament; 1-3 % by weight of a polyvinyl alcohol; 0.1-1 % by weight of a borate gelling agent; and 85-99 % by weight of sterile water. Suitable buffers are often needed to maintain the stated pH range for this system. This system requires the patient to administer the gel to the eye through a dispensing tip 1-3 times a day.

The instant invention differs from the system described in U.S. Patent No. 4,255,415 by being an ophthalmic medicament which is administered to the eye in liquid form as normal eye drops, but which liquid then gels after application to the eye to form a gelled carrier from which the ophthalmic drug is released in a controlled and sustained fashion. This method of application is facile and comfortable to ordinary patients thus combining this important feature of the instant invention with the desired controlled and sustained release of the ophthalmic drug at the desired site in the eye.

The object of the instant invention is to provide a topical ophthalmic medicament in liquid form which has improved biological response and increased duration of activity and a convenient and comfortable method of application and use thereof.

The instant invention pertains to a topical ophthalmic medicament delivery system in liquid form and administrable to the eye by introduction into the precorneal ocular cavity in a liquid drop form and then rapidly forming a transient gel in the eye allowing the gel to remain in the eye for a prolonged period of time to permit the sustained release of the active ophthalmic medicament onto the eye over a prolonged period, which medicament delivery system, with the % by weight based on the total weight of the delivery system, comprises

0.01 to 10 % by weight of an ophthalmic medicament;
1.5 to 9 % by weight of polyvinyl alcohol; with the provisio that, in case the delivery system comprises less than 4 % by weight of polyvinyl alcohol, it must comprise up to 2.5 % by weight of polyvinyl pyrrolidone;

0.1 to 2 % of boric acid; and
sterile deionized water, the liquid delivery system being maintained at a pH of 5.0 to 6.8.

A preferred delivery system comprises

0.01 to 10 % by weight of an ophthalmic medicament;
0.2 to 2.5 % by weight of polyvinyl pyrrolidone;
1.5 to 5 % by weight of polyvinyl alcohol;
0.1 to 2 % of boric acid; and
sterile deionized water, the liquid delivery system being maintained at a pH of 5.0 to 6.8.

A more preferred delivery system comprises

0.01 to 10 % by weight of an ophthalmic medicament;
4 to 9 % by weight of polyvinyl alcohol;
0.1 to 2 % of boric acid; and
79 to 95.89 % by weight of sterile deionized water, the liquid delivery system being maintained at a pH of 5.0 to 6.8.

Preferably the amount of the opthalmic medicament is from 0.01 to 1 % by weight; most preferably from 0.02 to 0.5% by weight.

Preferably the amount of polyvinyl alcohol is 5 to 8 % by weight; most preferably 5 to 7 % by weight.

Preferably the amount of boric acid is 0.2 to 1 % by weight; most preferably 0.3 to 0.7 % by weight.

Preferably the liquid is maintained at a pH of 5.5 to 6.7; most preferably at 6.0 to 6.5.

The instant invention also pertains to a method for treating ophthalmic disease, ailment or medical condition which comprises applying the liquid topical ophthalmic medicament described above as liquid drops to the eye.

Ophthalmic drugs suitable for incorporation into the liquid system of the instant invention include, but are not limited to, antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymixin, gramicidin, oxytetracycline, chloramphenicol, gentamicin, sisomicin,

penicillin and erythromycin; antibacterials such as sulfonamides, sulfacetamide, sulfamethiazole and sulfisoxazole; antivirals such as idoxuridine and vidarabine; other antibacterials such as nitrofurazone and sodium propionate; antiallergenics such as antazoline, methapyriline, chlorpheniramine, pyrilamine and prophenpyridamine; anti-inflammatories such as hydrocortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinoline, medrysone, prednisolone, methylprednislone, prednisolone 21-phosphate, prednisolone acetate, fluorometholone, betamethasone, betamethasone valerate, triamcinoline, indomethacin, flunixin and sodium diclofenac; decongestants such as phenylephrine, naphazoline and tetrahydrozaline; miotics and anticholinesterases such as pilocarpine, eserine salicylate, carbachol, diisopropyl fluorophosphate, phospholine iodide and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine and hydroxyamphetamine; and sympathomimetics such as epinephrine; particularly the anti-inflammatory sodium diclofenac or fluorometholone; or the miotic pilocarpine; most preferably sodium diclofenac.

The ophthalmic drug may be in the formulation in its base form or optionally in a salt form. Where a salt is utilized, the salt may be any eye-compatible, pharmaceutically acceptable acid addition salt.

The polyvinyl pyrrolidones (PVP) suitable for use in the instant invention have typically number average molecular weights in the range of 10,000 to 1,000,000. A preferred PVP used in the instant invention is referred to as PVP K 90 with an average molecular weight of about 360,000; a more preferred is referred to as PVP K 120 with an average molecular weight exceeding 360,000. The preferred PVP concentrations if used in the present invention are in the range of 0.2 to 2.5 % by weight, more preferably 0.5 to 2.0 %. If PVP is used in the present invention, it is always used in connection with polyvinyl alcohol.

The polyvinyl alcohols suitable for use in the instant invention have typically number average molecular weights in the range of 20,000 to 100,000 (weight average molecular weights in the range of 40,000 to 150,000) with a percent hydrolysis of at least 50%. Preferably the percent hydrolysis is at least 75 %; most preferably at least 88 %.

Polyvinyl alcohols are usually differentiated by the viscosity in centipoises of an aqueous 4 % solution measured at 20°C. The polyvinyl alcohols useful in the instant invention have viscosities of 6 to 75 cP; preferably 23 to 40 cP; most preferably 26 to 35 cP.

With increasing molecular weight, viscosity of aqueous solutions of PVA increases while

solubility in water decreases. With increased percent hydrolysis, hydrophilicity increases as more of the acetoxy groups are replaced by hydroxyl groups. Extraction of PVA with methanol will remove residual sodium acetate formed during the preparation of polyvinyl alcohol by the hydrolysis of poly(vinyl acetate).

Suitable additives may be incorporated into the liquid delivery system of the instant invention and include, but are not limited to, preservatives, stabilizers and tonicity enhancers.

Suitable preservatives are e.g. benzalkonium chloride, benzoxonium chloride, phenylmercuric acetate, phenylmercuric nitrate, chlorobutanol, phenylethyl or benzyl alcohol, methylparabene, chlorohexidine or thiomersal. The preservatives are typically present in an amount of 0.0001 to 1 % by weight, preferably in an amount of 0.001 to 0.5 %.

Suitable stabilizers in the instant invention are present up to 1 % by weight and are e.g. EDTA, disodium EDTA, sodium bisulfite, sodium metabisulfite or thiourea. More preferably the stabilizing agent is present in an amount of 0.01 to 0.2 % by weight.

Suitable tonicity enhancers in the instant invention are ionic and non-ionic tonicity enhancers. Representative ionic tonicity enhancers are e.g. NaCl, NaBr, LiCl, KCl, KBr, $CaCl_2$ or NaI. Non-ionic tonicity enhancers are e.g. urea, glycerol, sorbitol, propylene glycol or dextrose. The preferred amount of tonicity enhancing agent is the amount which is necessary to impart to the liquid delivery system an osmolality in the range of 100 to 400 mosmole, more preferably 200 to 350 mosmole and most preferably 300 mosmole.

The daily dosage of the ophthalmic drug system will depend on the patient's individual condition and the particular ophthalmic ailment disease state for which the drug system is being prescribed. Typically 0.05 to 0.8 ml of drug system will be administered 1-3 times per day.

The following examples are presented for the purpose of illustration only and are not to be construed to limit the nature or scope of the instant invention in any manner whatsoever.

Example 1

Polyvinyl Alcohol (PVA) Used in Drug Delivery System

PVA stock solutions are prepared by adding a appropriate amount of the PVA solid in a weighed amount of rapidly stirred deionized water. Normally 10 grams of PVA and 90 grams of water are used to form a 10% (w/w) solution. After the solid PVA is well dispersed at room temperature, the temperature of the flask, fitted with a condenser and containing the mixture, is raised to 85-95°C for at least 30 minutes to effect total solution of the PVA in the water. The solution is then allowed to cool to room temperature with continued stirring.

Representative PVA samples and their solution properties are described in the table below.

PVA	Source	Average MW (10^3)	Hydrol-ysis Percent	Visc. (4% soln) (cP)	Stock Soln Conc
VINOL® 350	Air Products	106-110	98+	62-72	10
POLYSCIENCES® #4398	Poly-sciences	≈125	88	--	10
POLYVIOL® 40/140	Wacker	≈100	86-89	40	10
AIRVOL® 325	Air Products	77-79	98+	28.5-32.5	10
MOVIOL® 26-88	Hoechst	--	88	26	10
VINOL® 523	Air Products	77-79	87-89	23-27	10
POLYVIOL® 25/190	Wacker	≈82	81-84	25	10

VINOL® 107	Air Products	22-31	98+	5.5-6.6	20
VINOL® 205	Air Products	22-31	87-89	5.2-6.2	20

The 10% stock solutions are generally clear, but tend to become opalescent on storage.

Example 2

Boric Acid Solutions Used in Drug Delivery System

Since the pH of PVA/boric acid solutions is below 6.0, formulations for ophthalmic use generally require pH adjustment. The addition of base directly to a PVA/boric acid solution causes localized gelation that interferes with efficient mixing needed during the pH adjustment. To overcome this problem, boric acid is titrated directly with base in the absence of PVA to prepare a slightly acidic boric acid before addition to the PVA solution. The titrated boric acid is much less basic than sodium hydroxide and when it is added to the PVA only a transient gel is formed which does not interfere with efficient mixing during the pH adjustment of the formulation. This process step is most important in carrying out the instant invention.

Because the interaction of boric acid and PVA causes a decrease in pH, the pH of the boric acid alone will be higher than the pH of the PVA/boric acid solution.

Concentrated stock solutions of boric acid with varying pH levels are prepared by reacting boric acid with dilute sodium hydroxide solutions as seen below.

Solution	pH	Boric Acid (%)	Sodium Hydroxide (N)
A	6.05	5.0	0.031
B	6.3	5.0	0.047
C	6.4	5.0	0.053
D	6.7	5.0	0.072

Example 3

Test Formulations

The ingredients in these formulations are combined on a weight basis, except for the boric acid stock solution which is added dropwise as a 5% (w/v) solution.

The following order of addition of ingredients minimizes the transient gelation observed during mixing of ingredients.

1. PVA solution;
2. sodium chloride and water;
3. titrated boric acid, dropwise with stirring; and
4. VOLTAREN® (see below), generally added after the above mixture has stood overnight.

Aqueous test formulations containing PVA, boric acid and VOLTAREN® (sodium diclofenac; sodium 2-(2,6-dichloroanilino)phenylacetate; antiinflammatory, Ciba-Geigy Corporation) are prepared with the content seen below. Water makes up the difference from the 100%.

PVA/Borate Ratio	5/0.5	5/1	10/0.75
PVA (%)	5.0	5.0	10.0
Boric Acid (%)	0.5	1.0	0.75
NaCl (%)*	0.575	0.45	0.34
NaOH (N)*	0.005	0.007	0.009
VOLTAREN® (%)	0.05	0.05	0.05

*NaCl is sodium chloride and is present to prepare an isotonic solution more compatible with tears found in the eye.

NaOH is sodium hydroxide present to form sodium borate and to adjust the pH to the desired level (pH is 6.4).

During steps 3 and 4 above, moderate heat (60-70°C) is applied to reduce viscosity to facilitate stirring and to disperse the transient gelation observed.

Example 4

Controlled Release of VOLTAREN® from Delivery System

A 20 ml beaker containing 0.6 g of freshly weighed test formulation, prepared as described in Example 3, is placed in a 35°C water bath on a magnetic stirrer-heater. To support a stirbar, a loop of plastic coated wire with a disk of polypropylene screen (Spectrum Lab Products, Macro Filter #46410) is suspended at the 10 ml level of the beaker and a small stirbar is placed on the screen. Stirring is begun at a defined rate of 150 rpm. At the start, 15 ml of warm (35°C) buffer (0.067 molar sodium-potassium phosphate, 0.075 molar sodium chloride; pH 7.35) is added to the beaker by running it gently against the beaker wall above the screen. Immediate gelling is observed upon addition of the buffer. Release is monitored by periodic sampling of the buffer from above the screen. The sample is then returned to the beaker after absorbance at 275 nm is measured. A final reading, taken after 18 hours, is taken to be 100 % release.

When a polyvinyl alcohol/boric acid formulation is so tested versus a control formulation containing no boric acid, the results are seen in the table below. (Ingredients levels are in weight percent units.)

Formulation	With Boric Acid	Without Boric Acid
Polyvinyl Alcohol (AIRVOL® 325)	6.0	6.0
Sodium Hydroxide	0.03	0.01
Boric Acid (adjusted to pH 6.4)	0.5	none
Sodium Chloride	0.575	0.81
VOLTAREN®	0.05	0.05

Release Time (minutes)
(at percent release)

50 (t_{50})	5	<< 2
100 (t_{100})	≥ 30	2

As can be seen from the data above, release of VOLTAREN® from the ungelled formulation (i.e. without boric acid) is extremely rapid and is virtually complete within two minutes. However, release of VOLTAREN® from the gelled formulation (with boric acid) is significantly prolonged.

Example 5

Controlled Release of VOLTAREN® from Delivery System

When an aqueous test formulation as described in Example 3 is administered to the eye of a patient, the VOLTAREN® is released at a sustained rate for a prolonged period of time.

Example 6

Test Formulations

The ingredients in these formulations are combined on a weight basis, except for the boric acid stock solution which is added dropwise as a 5% (w/v) solution.

The following order of addition of ingredients minimizes the transient gelation observed during mixing of ingredients.

1. PVA solution;
2. titrated boric acid, dropwise with stirring;
3. pilocarpine HCl, dissolved in water;
4. benzalkonium chloride; and
5. disodium EDTA.

Aqueous test formulations containing PVA, boric acid, pilocarpine hydrochloride, benzalkonium chloride and disodium EDTA are prepared with the content seen below. Water makes up the difference from the 100%.

Ingredients	%(wt/wt)	
PVA	5.0	5.0
boric acid	0.75	1.25
pilocarpine HCl	1.0	1.0
benzalkonium chloride	0.01	0.01
disodium EDTA	0.01	0.01

Example 7

Test Formulations

The ingredients in these formulations are combined on a weight basis, except for the boric acid stock solution which is added dropwise as a 5% (w/v) solution.
The following order of addition of ingredients minimizes the transient gelation observed during mixing of ingredients.

1. PVA solution;
2. sodium chloride and water;
3. polyvinyl pyrrolidone;
4. titrated boric acid, dropwise with stirring;
5. pilocarpine HCl, dissolved in water;
6. benzalkonium chloride; and
7. disodium EDTA.

Aqueous test formulations containing PVA, sodium chloride, polyvinyl pyrrolidone, boric acid, pilocarpine hydrochloride, benzalkonium chloride and disodium EDTA are prepared with the content seen below. Water makes up the difference from the 100%.

Ingredients	%(wt/wt)	
pilocarpine HCl	1.0	2.0
PVA	1.5	1.5
polyvinyl pyrrolidone	0.5	0.5
boric acid	0.75	0.75
benzalkonium chloride	0.01	0.01
disodium EDTA	0.01	0.01
sodium chloride	0.45	0

CLAIMS:

1. A topical ophthalmic medicament delivery system in liquid form and administrable to the eye by introduction into the precorneal ocular cavity in a liquid drop form and then rapidly forming a transient gel in the eye allowing the gel to remain in the eye for a prolonged period of time to permit the sustained release of the active ophthalmic medicament onto the eye over a prolonged period, which medicament delivery system, with the % by weight based on the total weight of the delivery system, comprises

0.01 to 10 % by weight of an ophthalmic medicament;
1.5 to 9 % by weight of polyvinyl alcohol; with the provisio that, in case the delivery system comprises less than 4 % by weight of polyvinyl alcohol, it must comprise up to 2.5 % by weight of polyvinyl pyrrolidone;
0.1 to 2 % of boric acid; and
sterile deionized water, the liquid delivery system being maintained at a pH of 5.0 to 6.8.

2. A delivery system according to claim 1, which comprises

0.01 to 10 % by weight of an ophthalmic medicament;
0.2 to 2.5 % by weight of polyvinyl pyrrolidone;
1.5 to 5 % by weight of polyvinyl alcohol;
0.1 to 2 % of boric acid; and
sterile deionized water, the liquid delivery system being maintained at a pH of 5.0 to 6.8.

3. A delivery system according to claim 1, which comprises

0.01 to 10 % by weight of an ophthalmic medicament;
4 to 9 % by weight of polyvinyl alcohol;
0.1 to 2 % of boric acid; and
79 to 95.89 % by weight of sterile deionized water, the liquid delivery system being maintained at a pH of 5.0 to 6.8.

4. A delivery system according to claim 1 wherein the amount of ophthalmic medicament is from 0.01 to 1 % by weight.

5. A delivery system according to claim 4 wherein the amount of ophthalmic medicament is from 0.02 to 0.5% by weight.

6. A delivery system according to claim 3 wherein the amount of polyvinyl alcohol is from 5 to 8 % by weight.

7. A delivery system according to claim 6 wherein the amount of polyvinyl alcohol is from 5 to 7 % by weight.

8. A delivery system according to claim 1 wherein the amount of boric acid is from 0.2 to 1 % by weight.

9. A delivery system according to claim 8 wherein the amount of boric acid is 0.3 to 0.7 % by weight.

10. A delivery system according to claim 1 wherein the pH is maintained at a pH of 5.5 to 6.7.

11. A delivery system according to claim 10 wherein the pH is maintained at a pH of 6.0 to 6.5.

12. A delivery system according to claim 1 wherein the percent hydrolysis of the polyvinyl alcohol is at least 50 %.

13. A delivery system according to claim 12 wherein the percent hydrolysis of the polyvinyl alcohol is at least 75 %.

14. A delivery system according to claim 13 wherein the percent hydrolysis of the polyvinyl alcohol is at least 88 %.

15. A delivery system according to claim 1 wherein the viscosity of an aqueous 4 % solution of the polyvinyl alcohol in centipoises as measured at 20°C is 6 to 75 cP.

16. A delivery system according to claim 15 wherein the viscosity is 23 to 40 cP.

17. A delivery system according to claim 16 wherein the viscosity is 26 to 35 cP.

18. A delivery system according to claim 1 wherein the ophthalmic medicament is sodium diclofenac, fluorometholone or pilocarpine.

19. A delivery system according to claim 1 wherein the ophthalmic medicament is sodium diclofenac.

20. A method of delivering a topical ophthalmic medicament to the eye which comprises introducing into the precorneal ocular cavity in liquid drop form a topical ophthalmic medicament delivery system according to claim 1.

21. An improved method of preparing an aqueous solution of polyvinyl alcohol and boric acid, with a pH in the range of 5.0 to 6.8, to prevent localized gelling upon mixing, for use in a drug delivery system of claim 1, which comprises

(a) titrating the boric acid solution with base to the desired pH level, and then
(b) adding dropwise the slightly acidic boric acid solution to a polyvinyl alcohol solution with stirring.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 93/10877

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/00 A61K47/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 255 415 (S.S.CHRAI) 10 March 1981 cited in the application see claims see column 2, line 43 - line 68 see column 3, line 1 - line 4	1-21
Y	EP,A,0 286 791 (AMERICAN CYANAMID) 19 October 1988 cited in the application see claims	1-21
Y	WO,A,89 06964 (INSITE VISION) 10 August 1989 cited in the application see claims see page 9, line 6 - line 25	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 March 1994	22. 03. 94

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Week 8231, Derwent Publications Ltd., London, GB; AN 82-64749E & JP,A,57 102 817 (KAKENYAKU KAKO) 26 June 1982 see abstract	1-21
Y	EP,A,0 386 960 (AMERICAN CYANAMID) 12 September 1990 see claims 1-22 see page 3, line 1 see page 3, line 47 - line 53 see page 5, line 21 see page 9, line 10 see page 9, line 34 - line 43	1-21
Y	EP,A,0 472 327 (SENJU) 26 February 1992 see claims 1,3,5-8,13,14	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 93/10877

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EP-A-0286791	19-10-88	GB-A- 2203039	12-10-88
		JP-A- 63253023	20-10-88
		US-A- 4888168	19-12-89
WO-A-8906964	10-08-89	DE-T- 68907545	28-10-93
		EP-A,B 0362321	11-04-90
		JP-T- 2503201	04-10-90
		US-A- 5192535	09-03-93
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		AU-B- 632539	07-01-93
		AU-A- 5076990	20-09-90
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		CA-A- 2048942	14-02-92
		CN-A- 1059725	25-03-92
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